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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,973	03/01/2002	Kesavan Esuvaranathan	488002000200	6742

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/086,973	ESUVARANATHAN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-16,18-31,33,34,36-41,43,44,46-57 and 59-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3-16,18-31,33,34,36-40,57 and 59-65* is/are allowed.

6)☒ Claim(s) *41,43,44 and 46-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 4/12/07.

Claims 1, 3-16, 18-31, 33, 34, 36-41, 43, 44, 46-57, and 59-65 remain pending and are under consideration.

Drawings

Applicant's drawing (Fig. 8B) submitted 4/12/07 overcame the previous objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 43, 44, and 46-56 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a superficial bladder tumor in the mucosal layer of the lumenal surface of a bladder by contacting the lumenal surface of the bladder with a transfection composition comprising (i) a polynucleotide; (ii) a cationic lipid, a cationic polymer or a dendrimer, or combinations thereof; and (iii) a solubilized cholesterol preparation comprising cholesterol solubilized with a cyclodextrin, wherein the polynucleotide is capable of expressing a protein selected from the group consisting of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony

stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell growth factor (VEGF), does not reasonably provide enablement for methods of treating bladder cancer in the muscular layer of the bladder, or for methods of treating superficial bladder cancer with nucleic acids encoding a tissue inhibitor of metalloproteinases (TIMP). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 41, 43, 44, and 46-56 are directed to methods of treating cancer of the bladder by intravesical administration of a composition comprising i) a polynucleotide that imparts anticancer activity against bladder cancer cells, ii) a cationic lipid, a cationic polymer or a dendrimer, or combinations thereof; and (iii) a solubilized cholesterol preparation, wherein the solubilized cholesterol preparation comprises cholesterol solubilized with a cyclodextrin.

The claims embrace any type of bladder cancer including superficial tumors and tumors of the muscular layer of the bladder.

Sutton (Mol. Ther. 2(3): 211-217, 2000) taught that administration of adenoviral vectors to the lumenal surface of the bladder resulted in transduction of only the most superficial layers of the bladder mucosa, and did not result in penetration to an intramuscular tumor. See abstract, and paragraph bridging columns 1 and 2 on page 214.

The instant specification showed that intravesical administration of cyclodextrin-solubilized cholesterol and nucleic acids resulted in transfection of the lumenal bladder

epithelium. See Figs. 6 and 10, and specification at page 33, lines 1-6, and page 33, line 21 to page 34, line 2.

Neither the prior art of record nor the specification provide evidence that nucleic acid or viral vectors can be delivered to cells beneath the lumenal bladder epithelium, such as smooth muscle cells, by intravesical administration.

The specification provided no guidance as to how to obtain transfection of tumors located beneath the lumenal bladder epithelium, e.g. in the muscle of the bladder, by contacting the lumenal surface of the bladder by intravesical administration.

In view of the state of the art regarding penetration of the nucleic acid vectors beyond the lumenal bladder epithelium, e.g. to the muscular layer of the bladder after intravesical administration, the inability to treat invasive tumors by intravesical administration of nucleic acids, the lack of a working example of such treatment in the specification, and a lack of guidance as to how to obtain transfection of cells beyond the epithelial layer by intravesical administration, one would have had to perform undue experimentation in order to practice the claimed method commensurate in scope with the claims, e.g. to treat tumors of the muscular layer of the bladder by administration of polynucleotides to the lumenal surface of the bladder by intravesical administration.

Regarding the list of proteins recited in claim 50, the specification is considered to be enabling for interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell

growth factor (VEGF), but not for a tissue inhibitor of metalloproteinases (TIMP) as broadly claimed.

A search of the prior art provided support for the use of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-18 (IL-18), interferon-alpha, interferon-beta, interferon-gamma, granulocyte-macrophage colony stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), p53, and an antagonist of vascular endothelial cell growth factor (VEGF) in the treatment of bladder cancer. However, the prior art did not support the use of a tissue inhibitor of metalloproteinases (TIMP) as broadly claimed. For example:

Grignon et al (Cancer Res. 56(7): 1654-1659, 1996) taught that TIMP expression is positively associated with tumor invasion and metastasis in many human cancers, and are associated with poor outcome in invasive bladder cancer. See abstract.

As the physiological art is considered to be unpredictable (MPEP 2164.03), the simple statement that these proteins are useful to treat bladder cancer is not considered to be enabling in the absence of some explanation of why they should be useful, particularly in view of the state of the art.

In view of the state and unpredictability of the art as discussed above, the absence of any relevant working example, and the absence of relevant guidance in the specification, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 4/12/07 have been fully considered but they are not persuasive.

Applicant asserts that the claimed methods are fully enabled, relying for support on Wu et al (2003), Wu et al (2004), and Brand (2002).

Regarding the scope of tumors, Applicant argues that the claimed methods result in transfection of superficial bladder epithelium as well as deeper layers of cells in a bladder tumor, relying for support on Fig. 4 of Wu(2003). This Figure shows that transfection is limited to the urothelium in normal bladders, but in bladders containing a superficial tumor, transfection was found in "deeper layers of the tumor". The authors explain this deeper penetration as having "more to do with the lack of proper organization of cells in the tumor mass than the GAG [glycosaminoglycan] layer." Accordingly, the penetration depended on the tumor being superficial in nature, i.e. being exposed to the bladder lumen. This result provides no support for the position that the claimed methods could be used to reach a bladder tumor that has arisen in the muscular layer of the bladder, behind the urothelium. Similarly, the experiment provides insufficient evidence to indicate that the claimed methods would be effective against an invasive tumor such as a transitional cell carcinoma, because the model a superficial tumor model. The Wu (2004) paper used the same model (see page 6978, column 2, first sentence of fourth full paragraph), so it is similarly unpersuasive.

Regarding the genus of polynucleotides that is enabled, Applicant argues that the claimed method can be practiced with a TIMP, relying for support on Brand (2002).

Brand was published after the time of filing, and so is not available to Applicant to establish the state of the art at the time of the invention. Furthermore, Brand provides evidence that the claims are not enabled for the broad scope of "a TIMP." Specifically, Brand taught that neither TIMP-3 nor TIMP-4 has any effect on cell proliferation. See page 258, column 2, third paragraph under **TIMPs and Proliferation**. Accordingly, the broad genus of "a TIMP" is not enabled. It is also not clear from Brand that the subgenus of TIMP-1 and TIMP-2 is enabled within the claimed context of bladder cancer. Table 1 on page 257 chows that TIMP-1 was increased in the urine of bladder cancer patients, and TIMP-2 was increased in the tumors of recurring bladder tumors. As noted in the rejection, Grignon taught that TIMP expression is positively associated with tumor invasion and metastasis in many human cancers, and is associated with poor outcome in invasive bladder cancer. See abstract. Table 2 of Brand lists a study in which tumor cells overexpressing TIMP-1 or TIMP-2 were transplanted to rat bladders that had been transplanted into the retroperitoneal space of mice. A marginal decrease in primary tumor growth, and significant decrease in tumor metastasis were observed. However, in view of the results in Table 1 and Grignon, the evidence of Table 2 is not persuasive of the enablement of the claimed methods, even if limited only to TIMP-1 and TIMP-2, because the art appears unpredictable in light of the totality of the evidence.

Further evidence of unpredictability comes from Brand's teaching that the literature disclosed four reports of growth promotion of cancer cells by TIMP-1, two reports showing no effect, and only one report showing an antiproliferative effect.

Regarding TimP-2, Brand cites six studies showing a proproliferative effect, two studies showing no effect, and six studies showing an antiproliferative effect. See page 258, column 2, first two paragraphs under **TIMPs and Proliferation**. This provides no clear evidence of the enablement of the claims for treating bladder cancer, and if anything supports the unpredictability of the claimed method.

For these reasons the rejection is maintained.

Conclusion

Claims 1, 3-16, 18-31, 33, 34, 36-40, 57, and 59-65 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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